Understanding cognitive heterogeneity in psychosis and high risk individuals
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INTRODUCTION
1. INTRODUCTION

1.1 The schizophrenia concept

Schizophrenic disorders are chronic and severe mental conditions that affect 26 million people worldwide and are the cause of moderate to severe disability in 60% of cases (Eaton et al., 2008). Due to their early onset and debilitating effects, schizophrenic disorders rank fifth among men and sixth among women as a leading cause of years lived with disability (Lora et al., 2012). Despite the diversity in pathogenesis, symptoms and course, the syndrome is invariably characterized by recurrent distortions in reality testing. These so-called “positive symptoms” relate to experiences such as hallucinations, delusions, bizarre behaviour and disorganization (APA, 2000). In addition, the clinical presentation of schizophrenia is characterized by the occurrence of (i) negative symptoms including avolition, affective flattening and social withdrawal, (ii) cognitive symptoms and (iii) affective symptoms (van Os and Kapur, 2009). Lifetime prevalence of schizophrenia is about 0.8-1% and incidence is 0.2-0.4 per 1000, with peak incidence during the third decade of life (Mueser and McGurk, 2004). Although prevalence is roughly equal in both sexes, women tend to have a later disease onset, better social functioning and a more favourable illness course (Mueser and McGurk, 2004). The high heritability (80%) of schizophrenia is not due to genetic influences per se but also to genotype-environment interactions that can be defined as “genetic control of sensitivity to environmental factors”, or as “environmental control of gene expression” (Kendler and Eaves, 1986). In a genotype–environment interaction, the disorder will tend to cluster in families not because of a direct genetic effect, but because relatives are more vulnerable to the risk-increasing effect of a prevalent environmental factor (van Os and Marcelis, 1998). Known environmental risk factors include pre- and perinatal factors, cannabis use, urbanicity and social isolation (Mueser and McGurk, 2004; van Os et al., 2010).

1.2 Cognitive functioning as core deficit in schizophrenia

Although cognitive deficits are not yet included in the diagnostic criteria for schizophrenia (APA, 2000), they are considered a core feature of schizophrenia symptomatology (Elvevag and Goldberg, 2000). More than a century ago, when schizophrenia was first defined in its current form, it was called dementia praecox, the focus being on the intellectual deterioration that accompanied the syndrome (Kraepelin, 1919). In the following years, the focus shifted to the more easily identifiable positive symptoms. During the past decade however, there has been a resurgence of interest in the cognitive alterations in patients with schizophrenia. This development may be explained by the notion that cognitive deficits are better predictors of functional outcome such as work performance and independent living than positive symptoms (Green et al., 2000; Harvey et al., 1998).

It has been found repeatedly that patients with a diagnosis of schizophrenia show a generalized impairment across a range of cognitive abilities including attention, processing speed, verbal learning and memory, working memory and executive functions (Elvevag and Goldberg, 2000; Mesholam-Gately et al., 2009; Heinrichs and Zakzanis, 1998). The degree of
impairment depends on the domain measured, with verbal memory and processing speed showing the largest deficits with effect sizes ranging from 1.3 to 1.6 (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009).

The neurodevelopmental model of schizophrenia suggests that cognitive deficits are a proximal manifestation of aberrant brain maturational processes that occur prior to the onset of the full clinical syndrome (Marenco and Weinberger, 2000). Likewise, children who will eventually develop schizophrenia exhibit subtle cognitive deficits of around -0.5 SD relative to their peers as early as seven years of age (Seidman et al., 2006; Keefe and Fenton, 2007). These cognitive deficits become more pronounced (around -1 SD) during the prodromal phase and first psychotic episode, after which they stabilize over the long-term course of the illness (Hoff et al., 2005; Lewandowski et al., 2011). Cognitive deficits have been associated with higher levels of negative symptoms, are at best marginally influenced by antipsychotic medication, and often persist despite complete resolution of positive symptoms (Szoke et al., 2008). Therefore, strategies are currently being developed to improve cognitive functions, either through pharmacological treatment or cognitive rehabilitation programmes.

1.3 Cognitive functioning in Genetic High Risk studies
Two major types of “high risk” strategies exist to better understand the development of psychosis and to improve detection and treatment strategies. The first is the genetic high risk approach, focusing on unaffected first-degree relatives of schizophrenia patients who have around 4 to 10% chance of developing the disease themselves (Gottesman, 1991). Generally, unaffected relatives display cognitive functioning intermediate to probands and healthy controls, with effect sizes ranging from 0.3 to 0.6 (Snitz et al., 2006; Seidman et al., 2010; Szoke et al., 2005). Largest effect sizes have been found on domains of verbal learning, sustained attention and semantic verbal fluency (Snitz et al., 2006) and effect sizes are comparable for offspring, siblings and parents.

These subtle cognitive deficits in unaffected relatives are currently considered as putative endophenotypes that might facilitate the identification of genetic factors involved in the vulnerability to schizophrenia (Gur et al., 2007). The endophenotype approach proposes that strictly defined neurobiological features of schizophrenia may reflect more direct expressions of genetic polymorphisms than clinical manifestations such as positive symptoms (Joyce and Roiser, 2007). Although several studies have identified putative cognitive endophenotypes, genetically sensitive studies that test the validity of these concepts have been limited so far.

1.4 Cognitive functioning in Ultra High Risk studies
The second type of high risk studies is a clinical approach identifying help-seeking adolescents or young adults who have not yet manifest psychosis, but subthreshold schizophrenia-like symptoms or other potentially prodromal signs. During the prodromal period, mood, cognitive, psychosocial and mild positive symptoms may appear (Yung et al.,
The most widely applied set of inclusion criteria for these kind of studies is defined by the ultra high-risk (UHR) approach and consists of (i) attenuated psychotic symptoms, (ii) brief intermittent psychotic symptoms, or (iii) a substantial drop in social/role functioning in conjunction with schizotypal personality disorder or a first-degree relative with psychotic disorder (Yung et al., 2005). Individuals who fulfil the UHR criteria have a 12-50% risk of developing psychosis within the following years (Yung et al., 2007). Cross-sectional UHR studies have consistently documented that neuropsychological deficits are intermediate between controls and first-episode psychosis patients, with effect sizes in the moderate range (Seidman et al., 2010; Simon et al., 2007). These deficits appear to be associated with functional disability in a manner parallel to that observed in established psychosis (Niendam et al., 2006). Additionally, it has been found that individuals in late prodromal stages show greater deficits compared with those in early prodromal stages (Simon et al., 2007). The issue however remains whether cognitive functioning may predict future transition to psychosis. While some studies found that UHR individuals who subsequently developed psychosis had worse cognitive performance at baseline in comparison to non-converters (Seidman et al., 2010; Eastvold et al., 2007), other studies did not confirm these results (Keefe et al., 2006; Hawkins et al., 2008). Longitudinal studies that compare cognitive functioning in UHR individuals who do and do not convert to psychosis have been limited by small samples and brief follow-up periods, which may have accounted for inconsistent results (Seidman et al., 2010).

1.5 Aim of the thesis
The overall aim of the studies described in this thesis was to increase our understanding of the variation in cognitive disturbances in psychosis and high risk populations. While cognitive impairment is present in most persons with schizophrenia, there is substantial inter-patient heterogeneity and this also holds for clinical and genetic high risk samples. Clarifying this phenotypic heterogeneity in the cognitive domain is needed to identify putative endophenotypes that may help to unravel the genetic background of the disorder, to improve psychosis prediction in at-risk individuals and to better direct treatment approaches towards specific patient groups. In the first part of this thesis we will examine how cognitive functioning is associated with different clinical variables. More specifically, associations will be studied between cognitive functioning and the two most frequently used substances (cannabis and stimulants), obsessive compulsive symptoms, and extrapyramidal symptoms. In the second part of this thesis the focus shifts to genetic and clinical high risk populations. Here we will address the impact of the cognitive impairment in patients with psychosis compared to their unaffected siblings and parents. Additionally we will investigate how level of functioning before the age of nineteen is linked to adult cognitive functioning in patients and their relatives. Furthermore, we will examine the size of the cognitive impairment in UHR individuals by the use of a standardized cognitive battery developed for schizophrenia. Finally we will examine whether combining structural MRI with a verbal fluency task may be of additional value for psychosis prediction in UHR subjects.
The following research questions will be addressed in this thesis:

PART I
Chapter 2: What is the association between current and lifetime cannabis use and cognitive functioning in patients with non-affective psychosis, their unaffected siblings and controls?
Chapter 3: What is the association between current and lifetime stimulant use and cognitive functioning in patients with non-affective psychosis, their unaffected siblings and controls?
Chapter 4: Is comorbid obsessive-compulsive symptomatology in patients with non-affective psychosis and their unaffected relatives associated with cognitive functioning?
Chapter 5: Are odour identification deficits in patients with non-affective psychosis associated with symptoms of parkinsonism?

PART II
Chapter 6: What is the size of the cognitive deficit in patients with psychosis compared to their unaffected first-degree relatives and healthy controls?
Chapter 7: What is the association between current cognitive functioning and adjustment to social and academic situations before the age of nineteen years in patients with non-affective psychosis and their unaffected siblings?
Chapter 8: Is the Dutch translation of the Measurement And Treatment Response Initiative to Improve Cognition in Schizophrenia (MATRICS) able to differentiate between patients with psychosis, UHR patients and healthy controls?
Chapter 9: Is the association between semantic verbal fluency performance and grey matter density different between UHR subjects that do and do not develop a psychotic disorder during follow-up?

REFERENCE LIST


prediction: 12-month follow up of a high-risk (“prodromal”) group. Schizophr Res. 60, 21-32.
